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Novel 9-(alkylthio)-Acenaphtho[1,2-e]-1,2,4-triazine derivatives: synthesis, cytotoxic activity and molecular docking studies on B-cell lymphoma 2 (Bcl-2)

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Abstract

Background and purpose of the study: Acenaphtho derivatives have been reported as antitumor agents. Due to this fact and also with the aim of developing the chemistry of potentially bioactive heterocyclic compounds via efficient reactions, a facile procedure for the synthesis of 9-(alkylthio)-acenaphtho[1,2-e]-1,2,4-triazines via two step condensation of thiosemicarbazide and acenaphtylene-9,10-quinone to form acenaphtho[1,2-e]-1,2,4-triazine-9(8H)-thiones and subsequent reaction with benzyl chloride derivatives is reported.

Methods: 9-(alkylthio) acenaphtho[1,2-e]-1,2,4-triazines were synthesized via the reaction of acenaphtho-9,10-quinone with thiosemicarbazide, and then with the benzyl chloride derivatives. Cytotoxicity of some prepared compounds was assessed through MTT assay on three different human cancerous cell lines (HL-60, MCF7, and MOLT-4 cells). Molecular docking studies were performed via AutoDock4.2 software in order to confirm an apoptosis-inducing activity of acenaphtho scaffolds via the Bcl-2 protein.

Results: Excellent yields of the products, short reaction times and simple work-up are attractive features of this synthetic protocol. The evaluated compounds exhibited moderate to good cytotoxic activities. Docking results on the active site of B-cell lymphoma 2 (Bcl-2) supported the experimental biological data and agreed well with previous *in silico* data for commonly used anti-cancer drugs. Moreover; results were analyzed considering binding efficiency indices.

Conclusions: The outcomes of the present study may be helpful in future targeting of Bcl-2 with the aim of developing apoptosis-inducing agents.

Keywords: Synthesis, Acenaphtho-9,10-quinone, Cytotoxic activity, Docking

Introduction

Economic generation of bioactive compounds has been a major concern in modern organic chemistry [1]. In this regard, development of novel compounds and especially diverse small molecule scaffolds caused higher attention of medicinal and biological chemists [2-4]. This can be attributed to the growing requirement in assembling libraries of structurally complex substances to be evaluated as hit/lead compounds in drug discovery projects.

Polycyclic aromatic hydrocarbon (PAH) heterocycles are highly important structural units in a variety of pharmacologically active substances [5-9]. At first glance, rigid polycyclic structures seem to have role in the development of antitumor agents owing to their ability in insertion between stacked base pairs of oligonucleotides and action as intercalator [10-12]. Particularly important is that when these planar polycyclic heterocycles bear appropriate side chains, further interactions with other important macromolecules might be envisaged [11,13].

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